Association of respiratory drive and effort with mortality and time to discharge in patients on mechanical ventilation in Canada: a longitudinal, prospective, registry-based cohort study

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Summary

Background Physiological data suggest that insufficient and excessive respiratory drive and effort during mechanical ventilation might injure the lung and diaphragm, but their clinical relevance is unknown.

Methods In this prospective, registry-based cohort study from the Toronto Intensive Care Observational Registry, we included all adults on mechanical ventilation admitted to the medical-surgical intensive care unit (ICU) at Toronto General Hospital from June 25, 2019, to April 1, 2022. There were no exclusion criteria. We obtained daily measurements of drive (airway occlusion pressure, $P_{0.1}$), effort (expiratory occlusion pressure, P_{occ}), lung stress during spontaneous breathing (dynamic transpulmonary driving pressure, $\Delta P_{L,dyn}$), and ventilator-delivered dynamic driving pressure ($\Delta P_{aw,dyn}$) for the first 10 days of mechanical ventilation. Daily hazards of death in ICU or discharge alive from ICU were quantified using Cox proportional hazards models adjusted for changing severity of illness over time.

Findings We included 1186 patients. 298 (25%) patients died during follow-up. $P_{0.1}$ and P_{occ} showed a non-linear association with the hazards of death and discharge alive ($p \leq 0 \cdot 024$). In patients with a ratio of arterial partial pressure of oxygen to inspired fraction of oxygen (PaO_2:FiO_2) of 150 mm Hg or less, both low and high levels of $P_{0.1}$ and P_{occ} were associated with lower rate of ICU discharge; when PaO_2:FiO_2 was greater than 150 mm Hg, higher $P_{0.1}$ and P_{occ} were associated with accelerated ICU discharge (interaction $p < 0 \cdot 0001$). High $\Delta P_{L,dyn}$ was associated with lower rate of ICU discharge ($p < 0 \cdot 0001$), especially when PaO_2:FiO_2 was less than 150 mm Hg. Higher effort magnified the association between $\Delta P_{aw,dyn}$ and rate of discharge alive (interaction $p = 0 \cdot 0052$).

Interpretation In patients on mechanical ventilation, insufficient or excessive respiratory drive and effort were associated with higher ICU mortality and lower rate of ICU discharge, particularly when oxygenation was more severely impaired. Elevated respiratory effort exacerbated the effect of ventilator-delivered driving pressure on outcome.

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Introduction

In respiratory failure, positive pressure ventilation supports or replaces the function of the respiratory muscles to sustain respiratory homeostasis. However, positive pressure ventilation can injure the lung,[1] diaphragm,[2] and brain,[3] and impair circulatory performance.[4] These adverse effects can be mediated in part by the action (or inaction) of the respiratory muscles.[5] Respiratory muscle inactivity during mechanical ventilation predisposes to diaphragm atrophy and pulmonary atelectasis.[6] At the same time, excessive respiratory drive and effort can cause lung injury,[7] diaphragm myotrauma,[8] patient–ventilator dyssynchrony,[9] excess oxygen consumption and cardiovascular demand,[10] and dyspnoea and psychological distress.[11] Maintaining an intermediate level of respiratory drive and effort might avoid these deleterious consequences and improve outcomes,[12] particularly in the presence of more severe lung injury.[7] However, current clinical practice guidelines for the management of mechanical ventilation in patients with acute respiratory failure do not make any recommendations regarding monitoring or targeting respiratory drive and effort.[13,14]

Recent advances in respiratory monitoring during mechanical ventilation permit routine non-invasive assessment of respiratory drive (airway occlusion pressure, $P_{0.1}$),[15] respiratory effort (expiratory occlusion pressure, P_{occ}), and dynamic lung stress during spontaneous breathing (dynamic transpulmonary driving pressure, $\Delta P_{L,dyn}$). These simply obtained measurements have been validated in three distinct cohorts and can be readily obtained at bedside on nearly all modern ventilators.[16–18] However, there are sparse data on the relationship between these parameters and patient outcomes.

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Research in context

Evidence before this study

We searched PubMed from database inception up to May 31, 2025, using search terms "acute hypoxemic respiratory failure", "mechanical ventilation", and "spontaneous breathing", to evaluate current data on the association between these variables and patient-centred outcomes. Physiological data suggest that both insufficient and excessive respiratory drive and effort during mechanical ventilation may injure the lung and diaphragm and impair haemodynamics. However, the clinical relevance of the patient's contribution to ventilation during mechanical ventilation (assessed by respiratory drive and effort) is unknown.

Added value of this study

This study found that daily measurements of respiratory drive and effort have a non-linear relationship with rates of death in the ICU and ICU discharge; both low and high values were associated with worse outcomes than intermediate values, particularly on days when patients had moderate to severe hypoxaemia (ratio of arterial partial pressure of oxygen to inspired fraction of oxygen ≤150 mm Hg or receiving extracorporeal life support). Increased respiratory effort exacerbated the association between driving pressure delivered by the ventilator and prolonged ICU admission, suggesting an interactive effect between the pressure delivered by the ventilator and the pressure generated by patient breathing effort. To our knowledge, this is the first study to report on the association of respiratory drive, respiratory effort, and their effect on lung-distending pressure with worse patient-centred outcomes.

Implications of all the available evidence

During invasive mechanical ventilation, the patient's contribution to ventilation could have an important influence on outcome; high patient respiratory effort may exacerbate the deleterious effect of injurious mechanical ventilation. Monitoring respiratory drive and effort during mechanical ventilation could detect risk for deterioration.

Our objective was to establish whether longitudinal measurements of $P_{0.1}$, P_{occ}, and $\Delta P_{L,dyn}$ during mechanical ventilation were associated with the rates of death or discharge alive in the intensive care unit (ICU). We hypothesised that intermediate values of $P_{0.1}$ and P_{occ} (similar to those seen in healthy individuals breathing at rest) would be associated with a lower risk of death in the ICU and an accelerated time to recovery, and that these associations would be more pronounced when lung function impairment was more severely impaired as quantified by the severity of hypoxaemia. By extension, we hypothesised that the magnitude of respiratory effort would modify the association between ventilator-delivered driving pressure and patient outcome.

Methods

Study design and participants

This prospective, longitudinal, registry-based cohort study was done using observational data from the Toronto Intensive Care Observational Registry (iCORE). iCORE includes all patients receiving invasive mechanical ventilation for 4 h or more in nine intensive care units (ICUs) affiliated with the University of Toronto (appendix p 3). For this analysis, we included patients admitted to the medical-surgical ICU at Toronto General Hospital who were receiving invasive mechanical ventilation between June 25, 2019, and April 1, 2022, as this was the only ICU enrolling patients in iCORE where measurements of $P_{0.1}$ and P_{occ} were routinely collected on a daily basis. The inclusion criteria were for participants to be aged 18 years or older and receive invasive mechanical ventilation in the ICU, regardless of ventilatory mode or presence of spontaneous breathing. For patients who were readmitted to the ICU during the same hospitalisation, we used only data from the first admission. There were no exclusion criteria. Because there is insufficient previous evidence to inform a formal sample size calculation, we opted for a pragmatic approach whereby we included all the available information. All data were de-identified before analysis.

See Online for appendix

Informed consent was waived by the Research Ethics Board of the University Health Network (authorisation number CAPCR ID for iCORE 21-5431) as all data in the iCORE registry are de-identified. This analysis of registry data was reviewed and approved by the research ethics board.

Procedures

Data on demographic and clinical variables, laboratory measurements, medications, and ventilator settings were extracted from iCORE. Extracted ventilator settings included mode of ventilation, set and total respiratory rate, tidal volume (V_T), peak airway pressure, positive end-expiratory pressure, and fraction of inspired oxygen.

Daily measurements of $P_{0.1}$ and P_{occ} for the first 10 days of mechanical ventilation (not collected in iCORE) and the inspiratory pressure delivered by the ventilator (dynamic driving pressure $\Delta P_{aw,dyn}$, computed as peak airway pressure minus positive end-expiratory pressure) were ascertained retrospectively by individual chart review for each patient. In the study ICU, $P_{0.1}$ and P_{occ} are measured daily in all patients receiving invasive mechanical ventilation. $P_{0.1}$ is collected directly from the ventilator screen or using a dedicated tool in the ventilator. P_{occ} is measured by performing an end-expiratory occlusion manoeuvre for the duration of a single breath (appendix p 7). Because this measurement does not require an end-inspiratory hold, it is less susceptible to artefact from expiratory muscle effort compared with the former method to estimate quasi-static airway driving pressure. We retrieved data on $\Delta P_{aw,dyn}$, $P_{0.1}$,

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	Full sample (n=1186)	Discharged alive by day 15 (n=633)	Censored (n=373)	ICU death by day 15 (n=180)
Age, years	57 (46–67)	60 (48–68)	55 (44–63)	57 (48–68)
Sex				
Female	411 (34·7%)	232 (37%)	120 (32%)	59 (33%)
Male	775 (65·3%)	401 (63%)	253 (68%)	121 (67%)
Reason for admission to ICU				
Acute hypoxaemic respiratory failure	429 (36·2%)	144 (23%)	210 (56%)	75 (42%)
Cardiac arrest	49 (4·1%)	12 (2%)	7 (2%)	30 (17%)
Chronic obstructive pulmonary disease	10 (0·8%)	6 (1%)	3 (1%)	1 (1%)
Cirrhosis	28 (2·4%)	5 (1%)	9 (2%)	14 (8%)
Neurological	15 (1·3%)	9 (1%)	4 (1%)	2 (1%)
Postoperative respiratory failure	445 (37·5%)	337 (53%)	84 (23%)	24 (13%)
Shock	123 (10·4%)	61 (10%)	34 (9%)	28 (16%)
Other	85 (7·2%)	57 (9%)	22 (6%)	6 (3%)
APACHE II score	16 (5)	15 (5)	16 (5)	19 (6)
Sequential organ failure assessment score	10 (2)	10 (2)	11 (2)	12 (2)
PaO_2:FiO_2	225 (144–316)	265 (192–346)	178 (118–254)	160 (107–247)
Tidal volume/predicted bodyweight	6 (2)	6 (2)	5 (2)	6 (2)
Positive end-expiratory pressure, cm H_2O	9 (4)	8 (3)	10 (3)	10 (4)
Dynamic driving pressure, cm H_2O	15 (5)	13 (4)	16 (6)	17 (7)
Estimated dynamic transpulmonary driving pressure, cm H_2O	20 (8)	18 (8)	23 (8)	22 (7)
Respiratory system compliance, mL per cm H_2O	25 (17–36)	30 (22–41)	19 (14–29)	21 (13–30)
Estimated dynamic lung compliance, mL per cm H_2O*	23 (16–32)	27 (20–36)	18 (12–26)	18 (13–26)
Airway occlusion pressure in the first 100 ms, $P_{0.1}$, cm H_2O	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Expiratory occlusion pressure, P_{occ}, cm H_2O	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)

Data are median (IQR), n (%), or mean (SD). ICU=intensive care unit. APACHE=acute physiology and chronic health evaluation. PaO_2:FiO_2=ratio of arterial partial pressure of oxygen to inspired fraction of oxygen. *Estimated dynamic transpulmonary driving pressure is only computed when inspiratory occlusion pressure is less than 0 cm H_2O.

Table: **Baseline participant characteristics and ventilator settings**

and P_{occ} at approximately 0800 h daily, the timepoint at which data in iCORE are routinely collected. Inspiratory muscle pressure (P_{mus}) was estimated as $-0{\cdot}75P_{occ}$ as previously validated.[16,17] $\Delta P_{L,dyn}$ was estimated as $\Delta P_{aw,dyn} - 0{\cdot}66P_{occ}$ for days when P_{occ} was less than 0 cm H_2O, as previously validated.[16,17] Dynamic respiratory system compliance[19,20] was computed as $V_T/\Delta P_{aw,dyn}$ on days when P_{occ} was 0 cm H_2O (ie, respiratory effort absent), and as $V_T/(\Delta P_{aw,dyn} + P_{mus})$ on days when P_{occ} was less than 0 cm H_2O (ie, respiratory effort present; appendix pp 3–4). Study participants were followed during the index ICU admission until death in the ICU or discharge from the ICU.

Statistical analysis

The primary outcomes were the competing events of death in ICU and discharge alive from the ICU. The primary objective of the analysis was to evaluate the associations between four different exposures ($P_{0.1}$, P_{occ}, $\Delta P_{L,dyn}$, and $\Delta P_{aw,dyn}$) and the competing and mutually exclusive events of death in the ICU or discharge alive from the ICU. Because different mechanisms could underlie these competing events and factors that affect the hazard of death might not necessarily affect the hazard of discharge alive (or vice versa), these outcomes were modelled using separate cause-specific hazard models to estimate the association between respiratory drive, effort, and dynamic stress and each event. The relationships between exposures and outcomes were assessed using extended cause-specific Cox proportional hazards models for time-dependent covariates, treating the exposure variables as continuous variables. The primary analysis evaluated the same-day effect of the exposures on the outcomes to reflect the clinical paradigm that ventilator settings and magnitude of respiratory effort influence the risk of lung and diaphragm injury contemporaneously. Exposures were evaluated by building a separate individual model for each variable reflecting separate but related hypotheses and to avoid multicollinearity. All models were adjusted for age, sex, daily sequential organ failure assessment score, daily number of hours receiving sedation (maximum of 24 h), number of sedatives infusing on a given day, daily dynamic compliance, and daily ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2:FiO_2). Because the influence of P_{occ} and $P_{0.1}$ on outcome was deemed likely to decrease as events became more remote in time from exposure, participants were censored if death in the ICU or ICU discharge did not occur within the week after the final longitudinal measurement. Cause-specific hazards were assessed by

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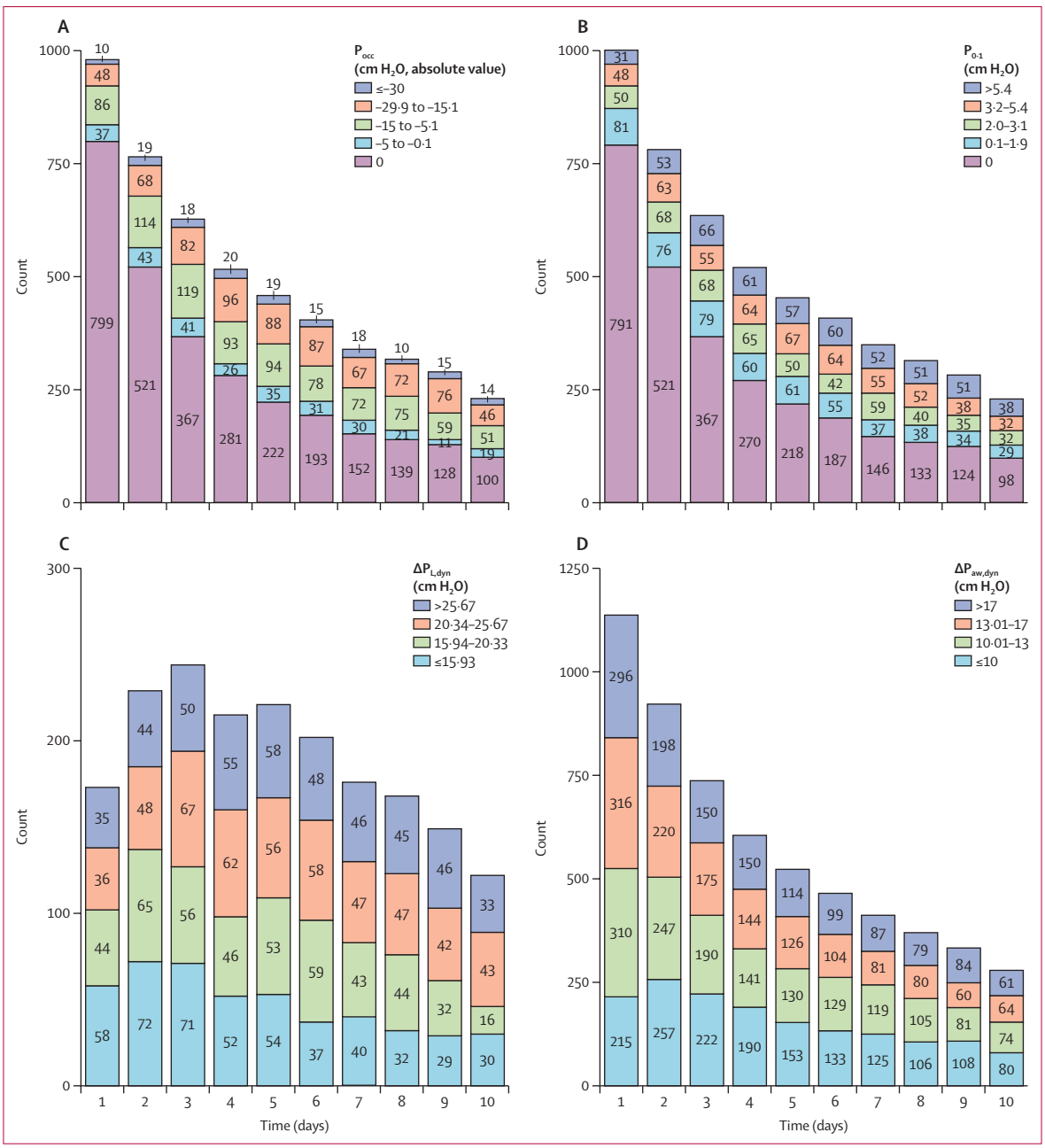

Figure 1: **Evolution of respiratory drive, respiratory effort, dynamic lung stress during spontaneous breathing, and dynamic driving pressure over the first 10 days of mechanical ventilation**

Distribution of categories of respiratory effort quantified by P_{occ} count (A), respiratory drive quantified by $P_{0.1}$ (B), dynamic lung stress during spontaneous breathing estimated by $\Delta P_{L,dyn}$ (C), and dynamic driving pressure delivered by the ventilator quantified by $\Delta P_{aw,dyn}$ (D). P_{occ} was categorised using predefined threshold values; $P_{0.1}$ was categorised using one category for zeroes, then quartiles for non-zeroes; and $\Delta P_{L,dyn}$ and $\Delta P_{aw,dyn}$ were categorised using quartiles. $P_{L,dyn}$ is only evaluable when P_{occ} is less than 0 cm H_2O. $\Delta P_{aw,dyn}$=dynamic driving pressure. $\Delta P_{L,dyn}$=estimated dynamic transpulmonary driving pressure. $P_{0.1}$=airway occlusion pressure. P_{occ}=expiratory occlusion pressure.

censoring patients with competing events. The time-dependent covariate input data were defined using the standard counting process notation.

Because we hypothesised a priori that both very low and very high values for $P_{0.1}$ and P_{occ} could be associated with worse outcomes, we prespecified that the potential non-linear functional form of the relationship between the exposures and the outcomes would be modelled using splines (appendix p 4).[21] We used penalised splines to mitigate the risk of overfitting from using user-defined knot positioning in the splines. Further, based on the a priori hypothesis that the effect of $P_{0.1}$ and P_{occ} on

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outcome was likely to be greater with more severe lung injury, we prespecified a test of interaction by severity of hypoxaemia, defining more severe hypoxaemia as PaO_2:FiO_2 of 150 mm Hg or less (the threshold for prone positioning) or receiving extracorporeal life support (ECLS) on any given day for each patient.[14] To address possible bias from the use of endogenous covariates in Cox models with time-varying covariates, we assessed the same associations over time using a pooled landmark modelling strategy and evaluated the risk of false discovery from endogenous covariates in simulation of a negative control scenario (appendix pp 4–5).[22]

We performed a number of sensitivity analyses on the primary modelling approach, including restricting analysis to days when respiratory effort was present, to patients who did not receive ECLS, to patient-days on ECLS, and excluding patients with a positive COVID-19 test in hospital (appendix pp 5–6). We also investigated lagged values of 3 days and 5 days for the exposures.

In a secondary analysis, we evaluated whether patient respiratory effort and dynamic driving pressure from the ventilator had synergistic effects on outcome by testing for an interaction between P_{occ} and $\Delta P_{aw,dyn}$ on mortality rate and ICU discharge rate.

In the primary analysis, missing exposure and outcome data were not imputed. Because missing exposure data were apparent (19% for P_{occ} and $P_{0.1}$ and 5% for $\Delta P_{aw,dyn}$), we performed an additional sensitivity analysis where values of P_{occ} and $P_{0.1}$ were censored after three consecutive days of missing values. We used R version 4.3.0 and the {survival}[21] package for the main statistical analysis.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication.

Results

Between June 25, 2019, and April 1, 2022, 1212 patients requiring invasive mechanical ventilation were admitted to the medical-surgical ICU at Toronto General Hospital. 26 patients were excluded due to missing exposure or outcome data, leaving 1186 participants with a total of 6118 patient-days of measurements. Of these, P_{occ} measurements were available for 4925 patient-days (1116 participants) and $P_{0.1}$ measurements were available for 4972 patient-days (1123 participants; appendix p 14). Baseline participant characteristics on admission to the ICU are presented in the table. Most patients were admitted for acute hypoxaemic respiratory failure or postoperative respiratory failure. 225 (19·0%) participants were on ECLS during their admission (total of 1340 patient-days of measurements while on ECLS). 205 (17·3%) participants were admitted with a positive test for COVID-19. 298 (25·1%) participants died in the ICU. The median duration of ICU admission in participants who survived in the ICU was 6 days (IQR 3–16). Data on missing observations for covariates included in the model are presented in the appendix (p 14). Mechanical ventilation parameters over the first 10 days of mechanical ventilation are reported in the appendix (p 14).

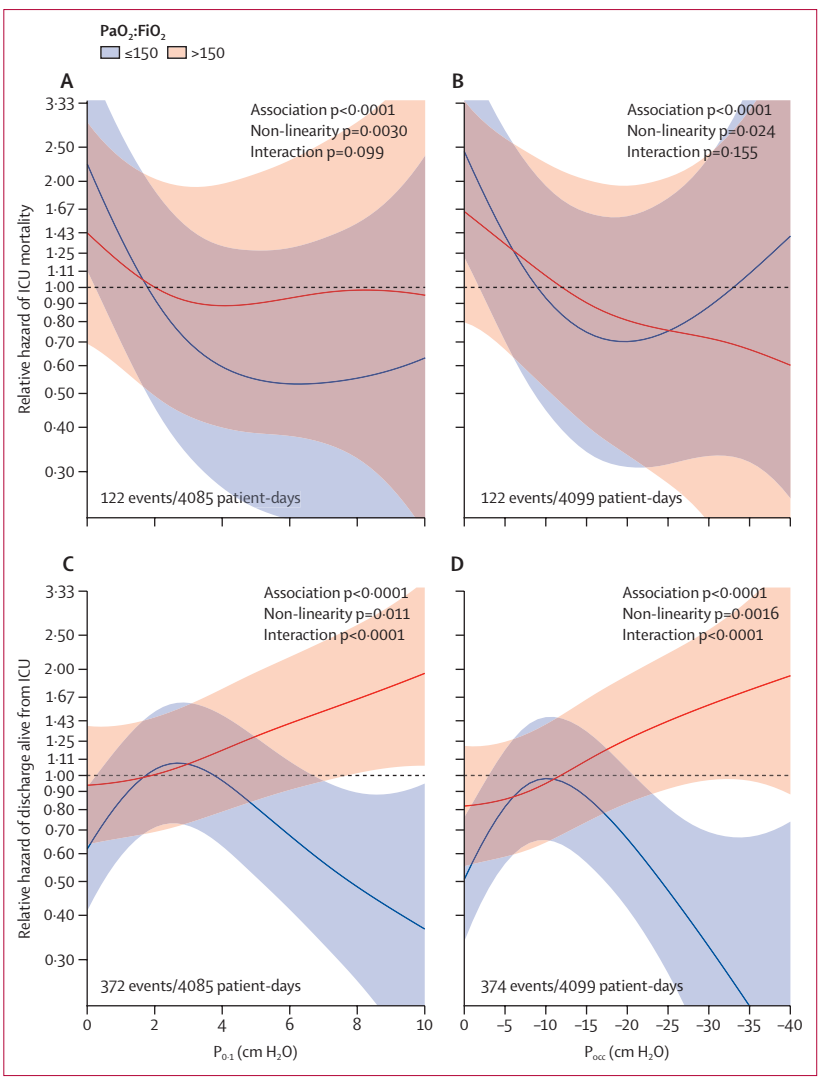

Figure 2: **Association of respiratory drive and respiratory effort with rate of ICU mortality and discharge alive**
Association of respiratory drive, $P_{0.1}$ (A), and respiratory effort, P_{occ} (B), with rate of ICU mortality; association of respiratory drive $P_{0.1}$ (C), and respiratory effort P_{occ} (D), with discharge alive from the ICU. Shaded areas represent 95% CIs. Bold lines represent median relative hazard. PaO_2:FiO_2≤150 mm Hg includes patient-days on extracorporeal life support. ICU=intensive care unit. $P_{0.1}$=airway occlusion pressure. P_{occ}=expiratory occlusion pressure. PaO_2:FiO_2=ratio of arterial partial pressure of oxygen to inspired fraction of oxygen.

The distributions of P_{occ}, $P_{0.1}$, $\Delta P_{aw,dyn}$, and $\Delta P_{L,dyn}$ over the first 10 days of mechanical ventilation are shown in figure 1. Respiratory drive and effort were absent at baseline (day 1) in most participants (799 [82%] of 980 for P_{occ} and 791 [79%] of 1001 for $P_{0.1}$) and were correlated within patients over time (intraclass correlation 0·24 for $P_{0.1}$ and 0·28 for P_{occ}). During days when respiratory effort was present (P_{occ}<0 cm H_2O), the most commonly

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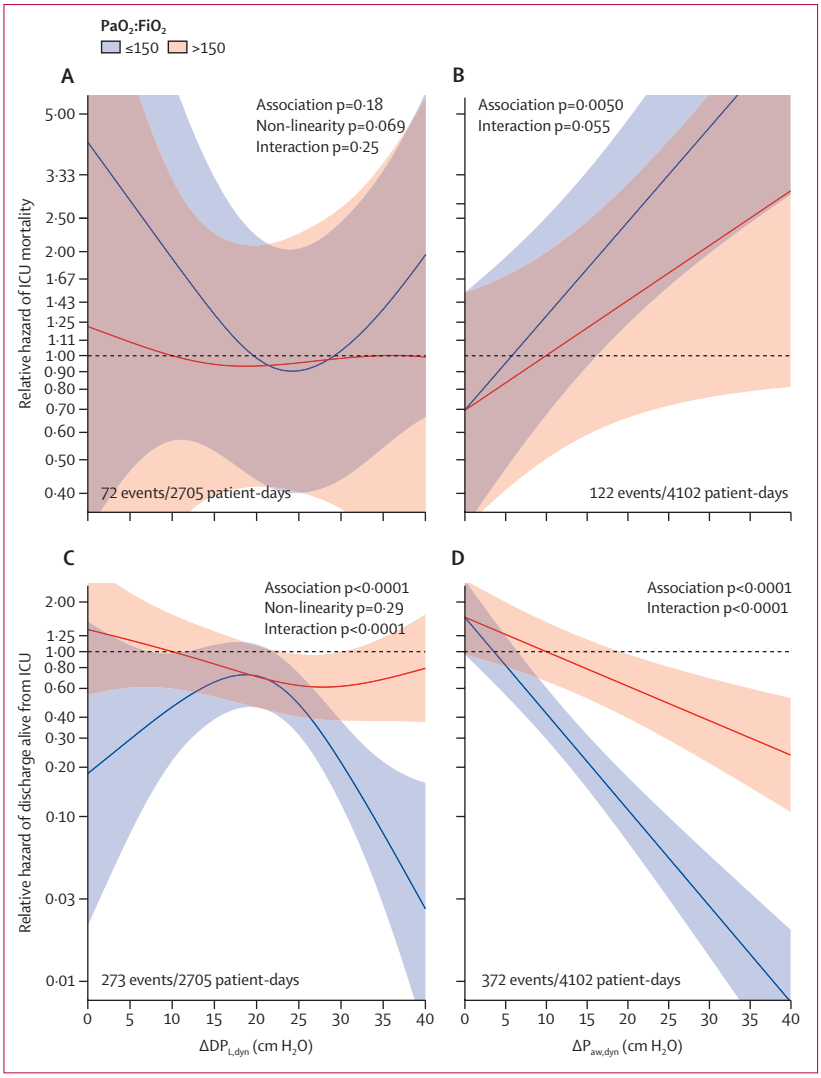

Figure 3: **Association of dynamic lung stress during spontaneous breathing and ventilator-delivered dynamic driving pressure with rate of ICU mortality and discharge alive**

Association of dynamic lung stress during spontaneous breathing, $\Delta P_{L,dyn}$ (A), and ventilator-delivered dynamic driving pressure, $\Delta P_{aw,dyn}$ (B), with rate of ICU mortality; association of dynamic lung stress during spontaneous breathing, $\Delta P_{L,dyn}$ (C), and ventilator-delivered dynamic driving pressure, $\Delta P_{aw,dyn}$ (D), with discharge alive from the ICU. Shaded areas represent 95% CIs. Bold lines represent median relative hazard. PaO_2:FiO_2≤150 mm Hg includes patient-days on extracorporeal life support. $\Delta P_{aw,dyn}$=dynamic driving pressure. $\Delta P_{L,dyn}$=estimated dynamic transpulmonary driving pressure. ICU=intensive care unit. PaO_2:FiO_2=ratio of arterial partial pressure of oxygen to inspired fraction of oxygen.

used modes were pressure-controlled ventilation and pressure support ventilation (appendix p 8).

$P_{0·1}$ and P_{occ} were associated with ICU mortality (p<0·0001) and these associations were non-linear in form (non-linearity p=0·0030 for $P_{0·1}$ and 0·024 for P_{occ}; figure 2A, B). The difference in these associations by severity of hypoxaemia did not reach statistical significance (interaction p=0·10 for $P_{0·1}$ and 0·15 for P_{occ}; figure 2A, B). The hazard of mortality was highest at very low values of $P_{0·1}$ and P_{occ}.

$P_{0·1}$ and P_{occ} were associated with the rate of discharge alive from ICU (p<0·0001) and these associations were non-linear in form (non-linearity p=0·011 for $P_{0·1}$ and 0·0016 for P_{occ}; figure 2C, D). These associations differed significantly by severity of hypoxaemia (interaction p<0·0001; figure 2C, D). When hypoxaemia was more severe, the hazard of discharge alive was highest at intermediate values of $P_{0·1}$ and P_{occ}. When hypoxaemia was less severe, higher $P_{0·1}$ and P_{occ} were associated with a higher rate of discharge alive (figure 2).

After restricting the analysis to days when respiratory effort was present (P_{occ}<0 cm H_2O), the associations between $P_{0·1}$ and P_{occ} and the hazard of discharge alive, and the interactions with severity of hypoxaemia, were still present (appendix p 9). After excluding participants who received ECLS from analysis, the associations between $P_{0·1}$ or P_{occ} and the hazard of mortality was amplified and the interactions with severity of hypoxaemia were statistically significant (appendix p 10).

The pattern of results was consistent with the primary analysis when excluding participants who tested positive for COVID-19, when restricting the analysis to participants with PaO_2:FiO_2 of 300 mm Hg or less (appendix p 11), when using different thresholds of PaO_2:FiO_2 for the interaction test with severity of hypoxaemia, and when values of $P_{0·1}$ and P_{occ} were censored after three consecutive days of missing values (appendix pp 15–18). When introducing a time lag of 3 days or 5 days between $P_{0·1}$ or P_{occ} and outcome, the association with the hazard of discharge alive persisted (appendix pp 15–18). The primary analysis using Cox survival models was replicated using a pooled landmark modelling strategy (appendix p 12). Simulating similar data structures where P_{occ} was unrelated to outcome (negative control) found a 3% type I error rate.

On days when participants were making spontaneous respiratory efforts (P_{occ}<0 cm H_2O), higher $\Delta P_{L,dyn}$ was associated with a lower hazard of discharge alive (association p<0·0001; figure 3C) but there was no association with mortality (p=0·18; figure 3A). The association between $\Delta P_{L,dyn}$ and the hazard of discharge alive was greater on patient-days with more severe hypoxaemia compared with patient-days with less severe hypoxaemia (interaction p<0·0001; figure 3C). There was no interaction between PaO_2:FiO_2 and $\Delta P_{L,dyn}$ on death (p=0·25). Similar results were obtained when excluding participants on ECLS (appendix p 13).

Higher $\Delta P_{aw,dyn}$ was associated with increased mortality (p=0·0050; figure 3B), although not after adjusting for P_{occ} (p=0·24; figure 4A, B). Higher $\Delta P_{aw,dyn}$ was associated with a lower hazard of discharge alive, and this association was greater on patient-days with more severe hypoxaemia compared with patient-days with less severe hypoxaemia (interaction p<0·0001 for PaO_2:FiO_2 of 150 mm Hg or less; figure 3D).

The magnitude of respiratory effort (P_{occ}) modified the association between $\Delta P_{aw,dyn}$ and the hazard rate of being discharged alive from the ICU (interaction p=0·0052; figure 4D). $\Delta P_{aw,dyn}$ was associated with a lower hazard

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of discharge alive when respiratory effort was higher (ie, more negative values of P_{occ}). Conversely, higher respiratory effort (more negative values of P_{occ}) was associated with a lower hazard of discharge alive when $\Delta P_{aw,dyn}$ was higher (figure 4C).

Discussion

In this longitudinal analysis of data from a prospective registry-based cohort study of patients on mechanical ventilation, insufficient and excessive respiratory drive and respiratory effort were associated with mortality and a reduced rate of ICU discharge. Consistent with our a priori hypothesis, the relationship between drive or effort and outcomes was non-linear, with the lowest rate of mortality and the highest rate of discharge alive from ICU observed at intermediate levels of drive and effort. Furthermore, dynamic lung stress from spontaneous breathing was associated with prolonged ICU admission, and larger respiratory efforts exacerbated the association between ventilator-delivered driving pressure and outcome. These associations differed according to the severity of hypoxaemia: when oxygenation was more severely impaired, higher respiratory drive and effort were associated with worse outcome in comparison to intermediate levels, whereas they were associated with better outcome when oxygenation was less severely impaired. Importantly, the association between high effort and worse outcomes persisted when considering only days in which patients had respiratory effort. This is, to the best of our knowledge, the first large-scale study to evaluate the time-varying effect of drive, effort, and lung-distending pressure on patient-centred outcomes in a longitudinal cohort of patients on mechanical ventilation. Taken together, these findings support the hypothesis that respiratory pressures generated by both the patient and the ventilator have an important influence on outcome. Monitoring respiratory drive and effort during mechanical ventilation could detect risk for deterioration.

Lung-protective ventilation is conventionally implemented by monitoring and targeting tidal volume, plateau pressure, and—more recently—driving pressure.[23,24] These parameters, however, fail to take account of the effect of the patient's own breathing on the injured lung, and do not predict the risk of other serious complications such as ventilator-induced diaphragm dysfunction. We found elevated respiratory effort amplifies the association between driving pressure and prolonged ventilation, suggesting that elevated respiratory effort could increase the risk of ventilator-associated lung injury. Potential mechanisms of harm from elevated respiratory effort include increased lung stress and strain, haemodynamic changes leading to increased lung oedema, larger dynamic negative swings in alveolar pressure, and pendelluft resulting in regional lung stress and lung injury. Notably, excessive respiratory effort can also lead to load-induced diaphragm injury.[25] On this basis, the focus of protective ventilation should be expanded to include not only the action of the ventilator (ie, driving pressure) but also that of the patient (ie, P_{occ}), especially when lung function is more severely impaired. $P_{0.1}$, P_{occ}, and $\Delta P_{L,dyn}$ can be measured non-invasively at the bedside using simple airway occlusion manoeuvres available on most contemporary ICU ventilators. Incorporating these assessments into routine assessment of patients on mechanical ventilation might help to identify patients at risk of poor clinical outcome and guide individualised adjustments in sedation or ventilatory support.[5] The data in this study also suggest a range of values for $P_{0.1}$

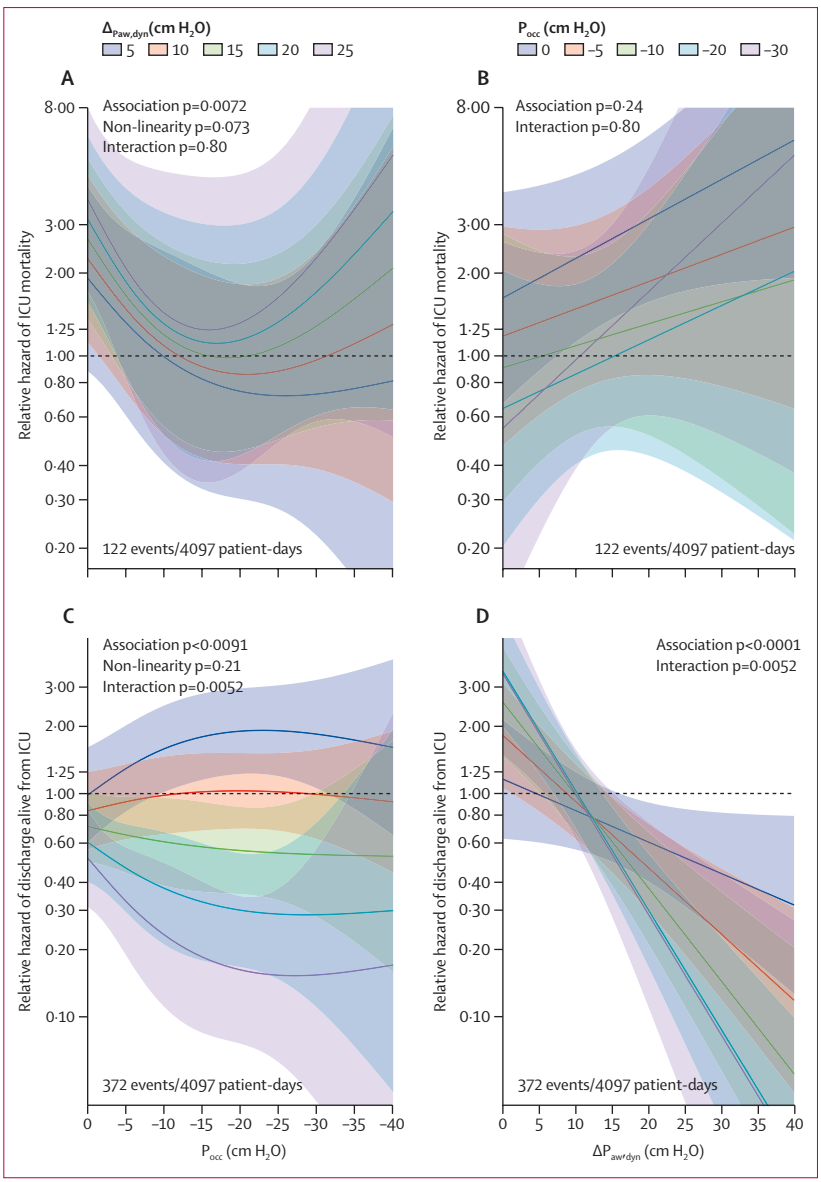

Figure 4: **Patient and ventilator interaction and association with rate of ICU mortality and discharge alive**
Ventilator-delivered dynamic driving pressure ($\Delta P_{aw,dyn}$) and patient respiratory effort (P_{occ}) exerted additive effects on mortality (A, B) and interactive effects on the rate of ICU discharge (C, D). Dotted lines and shaded areas represent 95% CIs. Bold lines represent median relative hazard. ICU=intensive care unit. P_{occ}=expiratory occlusion pressure. $\Delta P_{aw,dyn}$=dynamic driving pressure.

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(2 to 5 cm H_2O) and P_{occ} (–10 to –20 cm H_2O) that could be optimal to improve outcomes in patients on mechanical ventilation. These ranges align with those suggested based on physiological considerations.[26] Values outside this range could prompt reassessment of ventilatory support, sedation, or respiratory mechanics.

Although we cannot conclude that respiratory drive and effort have a causal effect on outcomes with this study design, various lines of evidence support the hypothesis that respiratory drive and effort have a causal influence on clinical outcomes. First, the observed results closely corroborate previously published predictions based on a substantial body of preclinical evidence;[26] the associations were non-linear, with optimal outcome at intermediate levels of drive and effort approximating those observed in healthy individuals, and appeared to be stronger in patients with more severely impaired lung function (consistent with previous experimental observations).[7] Second, the use of longitudinal data analysis to capture the time-varying exposure to insufficient or excessive drive and effort within patients can mitigate confounding by differences in severity of illness between patients.[22] The models were adjusted for time-varying exposure to key physiological markers of the severity of lung injury and multiorgan dysfunction. Our observations suggest that avoiding excessive respiratory drive and effort might be of benefit on days when hypoxaemia is severe; once lung function has recovered, elevated drive and effort were associated with higher rates of ICU discharge. The relevance of hypoxaemia to assessing the risk of lung injury is debated[27,28]—previous studies have not assessed for an interaction between hypoxaemia and driving pressure, although observational data support a qualitative distinction in lung injury at a PaO_2:FiO_2 threshold of 150 mm Hg.[27] Our findings suggest that increased lung stress could have a substantially greater influence on outcome when hypoxaemia is more severely impaired. Finally, the presence of an interaction between patient-generated pressures (P_{occ}) and ventilator-delivered pressures ($\Delta P_{aw,dyn}$) is best explained by their combined effects on lung stress.

Several limitations should be noted. First, this is a single-centre study from a tertiary centre, possibly limiting the generalisability of our findings. We also do not have data on ethnicity of the population, further limiting external validity. Second, treating clinicians were not blinded to these measurements, which could influence management of ventilation or sedation to alter outcomes. However, such an effect might tend to bias the results toward the null as intervening on insufficient or excessive respiratory drive would attenuate their impact on outcome. In the study centre, $P_{0.1}$ and P_{occ} are not employed to make decisions about liberation from mechanical ventilation. Third, the model adjusted for exposure to sedation but not for the type and dose of sedative drug. Residual confounding related to sedation management cannot be excluded. Fourth, $\Delta P_{L,dyn}$, as calculated in this study, incorporates both elastic and resistive components of the respiratory system and therefore does not represent static lung stress. Physiological considerations suggest that dynamic pressure swings might better reflect maximal regional lung stress.[29] Fifth, the sensitivity analyses performed cannot completely assess the viability of all model assumptions, such as the selection of lag duration. We applied a censoring rule for exposure variables after three consecutive days of missing data to reduce bias introduced by imputation assumptions. Nevertheless, if data were missing not at random—such as due to clinical deterioration—this approach could result in informative censoring. Sixth, using splines might increase the risk of overfitting. However, this is attenuated by the fact that non-linear fits were predicted a priori and prespecified before analysis, and by the use of penalised splines. Finally, ventilators use different methods to measure $P_{0.1}$, which could limit the accuracy of this variable. However, this variation represents a potential source of noise that would bias our results towards the null.

In summary, insufficient or excessive respiratory drive and effort during invasive mechanical ventilation are associated with higher ICU mortality and prolonged ICU admission, particularly when oxygenation is more severely impaired. Elevated patient respiratory effort during mechanical ventilation might exacerbate the effect of ventilator-delivered driving pressure on outcome.

Contributors

JD and ECG conceived and designed the study. JD and MAI acquired the data. JD and ECG verified the underlying data. JD, LEL, and ECG analysed and interpreted the data. JD drafted the manuscript. SS, IT, MU, LDS, MBPA, ASS, LB, NDF, and EF had access to the raw data and interpreted the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

De-identified data can be made available by reasonable request to the corresponding author.

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